Welcome to STN International * * * STN Columbus * * * *

FILE 'HOME' ENTERED AT 12:49:35 ON 08 JUL 2005

=> file reg

Uploading C:\Program Files\Stnexp\Queries\10743563.str

chain nodes :

11 12 13 14 15 16 18 19 20 21 23 24 27 28

ring nodes:
1 2 3 4 5 6 7 8 9 10

chain bonds :

 $9-11 \quad 10-24 \quad 11-12 \quad 11-27 \quad 12-13 \quad 12-14 \quad 14-28 \quad 15-18 \quad 15-16 \quad 15-29 \quad 19-20 \quad 20-21$

20-28 21-23 28-29

ring bonds :

1-2 1-6 2-3 3-4 4-5 4-7 5-6 5-10 7-8 8-9 9-10

exact/norm bonds :

4-7 5-10 7-8 8-9 9-10 9-11 10-24 11-27 12-13 12-14 14-28 15-18 15-16

19-20 21-23

exact bonds :

11-12 15-29 20-21 20-28 28-29

normalized bonds :

1-2 1-6 2-3 3-4 4-5 5-6

isolated ring systems :

containing 1 :

G1:0,N

G2:0,X

G3:Cy,Ak

Match level:

1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom

11:CLASS 12:CLASS 13:CLASS 14:CLASS 15:CLASS 16:CLASS 18:CLASS 19:CLASS

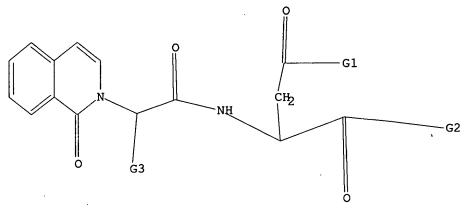
20:CLASS 21:CLASS 23:CLASS 24:CLASS 27:CLASS 28:CLASS 29:CLASS

STRUCTURE UPLOADED L1

=> dis 11

L1 HAS NO ANSWERS

L1 STR



G1 O, N

G2 O, X

G3 Cy,Ak

Structure attributes must be viewed using STN Express query preparation.

=> s 11 sam

L2 4 SEA SSS SAM L1

=> s l1 ful

L3 50 SEA SSS FUL L1

=> file caplus

FILE COVERS 1907 - 8 Jul 2005 VOL 143 ISS 3 FILE LAST UPDATED: 7 Jul 2005 (20050707/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s 13

L5

L4 6 L3

=> s 14 and pd< december 2002 22523224 PD< DECEMBER 2002 (PD<20021200)

1 L4 AND PD< DECEMBER 2002

=> s 14 not 15

L6 5 L4 NOT L5

=> dis 16 1-5 bib abs hitstr

L6 ANSWER 1 OF 5 CAPLUS COPYRIGHT 2005 ACS on STN

AN 2004:565214 CAPLUS

DN 141:106388

- TI Preparation of 4-oxo-3-(1-oxo-1H-isoquinolin-2-ylacetylamino)-pentanoic acid ester and amide derivatives as caspase inhibitors
- IN Charrier, Jean-Damien; Mortimore, Michael; Studley, John R.
- PA Vertex Pharmaceuticals Incorporated, USA
- SO PCT Int. Appl., 104 pp. CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

ran.		ENT 1	NO.			KIN	D	DATE		i	APPL:	ICAT:	ION I	NO.			ATE		
ΡI	PI WO 2004058718			A1 20040715		WO 2003-US40870													
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			co,	CR,	CU,	CZ,	DE,	DK,	DM,	DZ,	EC,	EE,	ES,	FI,	GB,	GD,	GE,	GH,	
			GM,	HR,	HU,	ID,	IL,	IN,	IS,	JP,	KE,	KG,	KP,	KR,	KZ,	LC,	LK,	LR,	
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			PL,	PT,	RO,	RU,	SD,	SE,	SG,	SK,	SL,	ТJ,	TM,	TN,	TR,	TT,	TZ,	UA,	
			UG,	US,	UZ,	VN,	YU,	ZA,	ZM,	ZW									
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			ES,	FI,	FR,	GB,	GR,	HU,	ΙE,	IT,	LU,	MC,	NL,	PT,	RO,	SE,	SI,	SK,	
			TR,	BF,	ВJ,	•		•	•	•	•		•	•	•	•		TD,	ΤG
	US 2004192612		A1		20040930		US 2003-743563			20031222									
PRAI	US	2002	-435	133P		P		2002	1220										
os GI	MAF	RPAT	141:	1063	88						•								

- AB The title compds. of formula I [X = alkoxy, (substituted) NH2, etc.; Y = halo, trifluorophenoxy, tetrafluorophenoxy; R1 = alkyl; R2, R3 = H, halo, OCF3, CN, CF3] are prepared The present invention also provides pharmaceutical compns. and methods using such compns. for treating a caspase-mediated disease, particularly in the central nervous system. Thus, II was prepared from 7-chloroisochromen-1-one (preparation given), (S)-2-aminobutyric acid tert-Bu ester and 3-amino-5-fluoro-4-hydroxypentanoic acid tert-Bu ester.
- IT 640286-59-5P 721397-83-7P

RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

(preparation of (oxoisoquinolinylacetylamino)-oxopentanoic acid ester and amide derivs. as caspase inhibitors)

RN 640286-59-5 CAPLUS

CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-5-fluoro-4-oxo-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 721397-83-7 CAPLUS

CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-4-oxo-5-(2,3,5,6-tetrafluorophenoxy)-, 1,1-dimethylethylester, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

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TT 721397-79-1P 721397-80-4P 721397-81-5P
721397-82-6P 721397-84-8P 721397-85-9P
721397-86-0P 721397-87-1P 721397-88-2P
721397-89-3P 721397-90-6P 721397-91-7P
721397-92-8P 721397-93-9P 721397-94-0P
721397-95-1P 721397-96-2P 721397-97-3P
721397-98-4P 721397-99-5P 721398-00-1P
721398-01-2P 721398-02-3P 721398-03-4P
721398-04-5P 721398-05-6P 721398-06-7P
721398-07-8P 721398-08-9P 721398-09-0P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
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(preparation of (oxoisoquinolinylacetylamino)-oxopentanoic acid ester and amide derivs. as caspase inhibitors)

RN 721397-79-1 CAPLUS

CN Pentanoic acid, 5-fluoro-4-oxo-3-[[(2S)-1-oxo-2-(1-oxo-2(1H)-isoquinolinyl)butyl]amino]-, 1,1-dimethylethyl ester (9CI) (CA INDEX

NAME)

Absolute stereochemistry.

RN 721397-80-4 CAPLUS

CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-3-methyl-1-oxobutyl]amino]-5-fluoro-4-oxo-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 721397-81-5 CAPLUS

CN Pentanoic acid, 5-fluoro-4-oxo-3-[[(2S)-1-oxo-2-(1-oxo-2(1H)-isoquinolinyl)pentyl]amino]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 721397-82-6 CAPLUS

CN Pentanoic acid, 5-fluoro-4-oxo-3-[[(2S)-1-oxo-2-[1-oxo-7-(trifluoromethyl)-

2(1H)-isoquinolinyl]butyl]amino]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 721397-84-8 CAPLUS

CN Pentanoic acid, 4-oxo-3-[[(2S)-1-oxo-2-[1-oxo-7-(trifluoromethyl)-2(1H)-isoquinolinyl]butyl]amino]-5-(2,3,5,6-tetrafluorophenoxy)-, 1,1-dimethylethyl ester, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 721397-85-9 CAPLUS

CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-5-fluoro-4-oxo-, ethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 721397-86-0 CAPLUS

CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-5-fluoro-4-oxo-, propyl ester (9CI) (CA INDEX NAME)

RN 721397-87-1 CAPLUS

CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-5-fluoro-4-oxo-, 3,3,3-trifluoropropyl ester (9CI) (CAINDEX NAME)

Absolute stereochemistry.

RN 721397-88-2 CAPLUS

CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-5-fluoro-4-oxo-, 1-methylethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 721397-89-3 CAPLUS

CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-5-fluoro-4-oxo-, phenylmethyl ester (9CI) (CA INDEX NAME)

RN 721397-90-6 CAPLUS

CN Pentanoic acid, 4-oxo-3-[[(2S)-1-oxo-2-(1-oxo-2(1H)-isoquinolinyl)butyl]amino]-5-(2,3,5,6-tetrafluorophenoxy)-, 1,1-dimethylethyl ester, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 721397-91-7 CAPLUS

CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-4-oxo-5-(2,3,5,6-tetrafluorophenoxy)-, methyl ester, (3S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 721397-92-8 CAPLUS

CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-4-oxo-5-(2,3,5,6-tetrafluorophenoxy)-, ethyl ester, (3S)-(9CI) (CA INDEX NAME)

RN 721397-93-9 CAPLUS

CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-4-oxo-5-(2,3,5,6-tetrafluorophenoxy)-, propyl ester, (3S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 721397-94-0 CAPLUS

CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-4-oxo-5-(2,3,5,6-tetrafluorophenoxy)-, 3,3,3-trifluoropropyl ester, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 721397-95-1 CAPLUS

CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-4-oxo-5-(2,3,5,6-tetrafluorophenoxy)-, 1-methylethyl ester, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 721397-96-2 CAPLUS

CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-4-oxo-5-(2,3,5,6-tetrafluorophenoxy)-, phenylmethyl ester, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 721397-97-3 CAPLUS

CN Pentanoic acid, 3-[[(2S)-2-(6-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-5-fluoro-4-oxo-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 721397-98-4 CAPLUS

CN Pentanoic acid, 5-fluoro-4-oxo-3-[[(2S)-1-oxo-2-[1-oxo-6-(trifluoromethyl)-2(1H)-isoquinolinyl]butyl]amino]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

RN 721397-99-5 CAPLUS

CN Pentanoic acid, 3-[[(2S)-2-(6,7-dichloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-4-oxo-5-(2,3,5,6-tetrafluorophenoxy)-, 1,1-dimethylethyl ester, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 721398-00-1 CAPLUS

CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-4-oxo-5-(2,3,5,6-tetrafluorophenoxy)-, cyclohexyl ester, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 721398-01-2 CAPLUS

CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-4-oxo-5-(2,3,5,6-tetrafluorophenoxy)-, cyclopentyl ester, (3S)- (9CI) (CA INDEX NAME)

RN 721398-02-3 CAPLUS

Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-4-oxo-5-(2,3,5,6-tetrafluorophenoxy)-, tetrahydro-2H-pyran-4-yl ester, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 721398-03-4 CAPLUS

CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-4-oxo-5-(2,3,5,6-tetrafluorophenoxy)-, 2-methylpropylester, (3S)- (9CI) (CA INDEX NAME)

RN 721398-04-5 CAPLUS

CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-4-oxo-5-(2,3,5,6-tetrafluorophenoxy)-, 1-ethylpropyl ester, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 721398-05-6 CAPLUS

CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-4-oxo-5-(2,3,5,6-tetrafluorophenoxy)-, cycloheptyl ester, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 721398-06-7 CAPLUS

CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-4-oxo-5-(2,3,5,6-tetrafluorophenoxy)-, 1,2-dimethylpropylester, (3S)- (9CI) (CA INDEX NAME)

RN 721398-07-8 CAPLUS

CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-4-oxo-5-(2,3,5,6-tetrafluorophenoxy)-,
1-methyl-1-phenylethyl ester, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 721398-08-9 CAPLUS

CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-4-oxo-5-(2,3,5,6-tetrafluorophenoxy)-, 1,1-dimethyl-2-propynyl ester, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 721398-09-0 CAPLUS

CN 2(1H)-Isoquinolineacetamide, 7-chloro- α -ethyl-N-[(1S)-1-[2-(methoxymethylamino)-2-oxoethyl]-2-oxo-3-(2,3,5,6-tetrafluorophenoxy)propyl]-1-oxo-, (α S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

IT 618459-84-0P 640286-42-6P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of (oxoisoquinolinylacetylamino)-oxopentanoic acid ester and amide derivs. as caspase inhibitors)

RN 618459-84-0 CAPLUS

CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-5-fluoro-4-oxo- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 640286-42-6 CAPLUS

CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-4-oxo-5-(2,3,5,6-tetrafluorophenoxy)-, (3S)- (9CI) (CA INDEX NAME)

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L6
     ANSWER 2 OF 5 CAPLUS COPYRIGHT 2005 ACS on STN
AN
     2004:20662 CAPLUS
     140:77410
DN
     Preparation of isoquinolinone and quinazolinone peptide derivatives as
ΤI
     caspase inhibitors
     Knegtel, Ronald; Mortimore, Michael; Studley, John; Millan, David
IN
     Vertex Pharmaceuticals Incorporated, USA
PA
SO
     PCT Int. Appl., 95 pp.
     CODEN: PIXXD2
DT
     Patent
     English
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     PATENT NO.
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     WO 2004002961
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PRAI US 2002-392592P
                             Ρ
                                    20020628
                             Ρ
     US 2002-435073P
                                    20021220
                                    20030627
     WO 2003-US20557
                             W
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     MARPAT 140:77410
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AB The invention relates to isoquinolinones and quinazolinones I [X is CH or N; Y is halo, tri- or tetrafluorophenoxy; R2 is alkyl; R3 is H, halo, OCF3, CN, or CF3; R4 is groups R3 or alkylthio, (un)substituted Ph, phenoxy, or phenylthio; with the proviso that when Y is halo, then R3 and

R4 are not both H] which are caspase inhibitors useful in compns. for the treatment of various diseases, conditions, or disorders. Thus, I (X = CH, Y = F, R2 = Et, R3 = H, R4 = Cl), prepared by coupling of (S)-2-(7-chloro-1-oxo-1H-isoquinolin-2-yl)butyric acid (preparation given) with 3-amino-5-fluoro-4-hydroxypentanoic acid tert-Bu ester, had Ki (M-1 s-1) > 500,000 for inhibition of caspase-1 or caspase-3, Ki 100,000-500,000 for inhibition of caspase-8, and IC50 < 1 μM for inhibition of interleukin-1 β secretion.

IT 618459-84-0P 618460-05-2P 618460-11-0P 618460-12-1P 640286-34-6P 640286-35-7P 640286-42-6P 640286-43-7P 640286-48-2P 640286-49-3P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of isoquinolinone and quinazolinone peptide derivs. as caspase inhibitors)

RN 618459-84-0 CAPLUS

CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-5-fluoro-4-oxo- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 618460-05-2 CAPLUS

CN Pentanoic acid, 5-fluoro-4-oxo-3-[[(2S)-1-oxo-2-[1-oxo-7-(trifluoromethyl)-2(1H)-isoquinolinyl]butyl]amino]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 618460-11-0 CAPLUS

CN Pentanoic acid, 5-fluoro-4-oxo-3-[[(2S)-1-oxo-2-(1-oxo-7-phenyl-2(1H)-isoquinolinyl)butyl]amino]- (9CI) (CA INDEX NAME)

RN 618460-12-1 CAPLUS

CN Pentanoic acid, 4-oxo-3-[[(2S)-1-oxo-2-(1-oxo-2(1H)-isoquinolinyl)butyl]amino]-5-(2,3,5,6-tetrafluorophenoxy)-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 640286-34-6 CAPLUS

CN Pentanoic acid, 3-[[(2S)-2-(6-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-5-fluoro-4-oxo- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 640286-35-7 CAPLUS

CN Pentanoic acid, 5-fluoro-4-oxo-3-[[(2S)-1-oxo-2-[1-oxo-6-(trifluoromethyl)-2(1H)-isoquinolinyl]butyl]amino]- (9CI) (CA INDEX NAME)

RN 640286-42-6 CAPLUS

CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-4-oxo-5-(2,3,5,6-tetrafluorophenoxy)-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 640286-43-7 CAPLUS

CN Pentanoic acid, 3-[[(2S)-2-(6,7-dichloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-4-oxo-5-(2,3,5,6-tetrafluorophenoxy)-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 640286-48-2 CAPLUS

CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-3-methyl-1-oxobutyl]amino]-5-fluoro-4-oxo- (9CI) (CA INDEX NAME)

RN 640286-49-3 CAPLUS

CN Pentanoic acid, 4-oxo-3-[[(2S)-1-oxo-2-[1-oxo-7-(trifluoromethyl)-2(1H)-isoquinolinyl]butyl]amino]-5-(2,3,5,6-tetrafluorophenoxy)-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

$$F_3C$$

$$O$$

$$Et$$

$$O$$

$$F$$

IT 640286-59-5P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of isoquinolinone and quinazolinone peptide derivs. as caspase inhibitors)

RN 640286-59-5 CAPLUS

CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-5-fluoro-4-oxo-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2005 ACS on STN AN 2003:991174 CAPLUS

DN 140:28050

TI Synthesis of peptide heterocyclic derivatives as caspase inhibitors

IN Golec, Julian M. C.; Charifson, Paul S.; Charrier, Jean-Damien; Binch, Hayley

PA UK

SO U.S. Pat. Appl. Publ., 28 pp.

CODEN: USXXCO

DT Patent

LA English

FAN.CNT 1

GΙ

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	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
ΡI	US 2003232846	A 1	20031218	US 2002-166437	20020610	
PRAI	US 2002-166437		20020610			
os	MARPAT 140:28050					

$$\begin{array}{c|c}
 & \circ & \circ \\
 & & \downarrow \\
 &$$

AB Compds. I and their synthesis are claimed [R1 = H, CN, CHN2, (substituted)alkyl, aryl, non-aromatic heterocycle, etc.; R2 = CH2COOH, CO2H (or ester/amide/isosteres of); R3 = H or alkyl; X1, X3 = N or C; X2 = bond, O, S, N or C wherein any X with suitable valence may bear a substituent; each C in ring A may also be substituted; ring A substituents = H, halo, alkyl, aryl, OH, CN, etc.; A may also bear a fused ring]. Over 20 synthetic examples are given. Thus, substitution of bromoacetic acid Et ester with the corresponding isoquinolone followed by saponification and coupling to 3-amino-5-fluoro-4-hydroxypentanoic acid tert-Bu ester provided the hydroxy ester intermediate. Oxidation of the hydroxy ester followed by treatment with TFA yielded II as a white powder. Compds. of the invention are caspase inhibitors; data is provided for caspase-1,-3,-7 and caspase-8 inhibition (Ki). Also determined was inhibition of $IL-1\beta$ secretion from peripheral blood mononuclear cells and activity in a Fas ligand induced apoptosis assay. Compound II had Ki (M-1 s-1) of 248,000 for caspase-1, 130,000 for caspase-3 and an IC50 of 2.9 μM for IL-1 β secretion. Compds. I may be used as a component of immunotherapy for the treatment of cancer.

IT 344461-03-6P 344461-10-5P

RL: BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(synthesis of peptide heterocyclic derivs. as caspase inhibitors)

RN 344461-03-6 CAPLUS

CN Pentanoic acid, 5-fluoro-4-oxo-3-[[(2S)-1-oxo-2-(1-oxo-2(1H)-isoquinolinyl)propyl]amino]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 344461-10-5 CAPLUS

CN Benzoic acid, 2,6-dichloro-, (3S)-4-carboxy-2-oxo-3-[[1-oxo-2-(1-oxo-2(1H)-isoquinolinyl)propyl]amino]butyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

IT 344461-30-9P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(synthesis of peptide heterocyclic derivs. as caspase inhibitors)

RN 344461-30-9 CAPLUS

CN Benzoic acid, 2,6-dichloro-, (3S)-5-(1,1-dimethylethoxy)-2,5-dioxo-3-[[1-oxo-2-(1-oxo-2(1H)-isoquinolinyl)propyl]amino]pentyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

L6 ANSWER 4 OF 5 CAPLUS COPYRIGHT 2005 ACS on STN

AN 2003:855766 CAPLUS

```
DN
     139:345913
     Identification of tumor necrosis factor \alpha (TNF-\alpha) modulator
TI
     compounds, and use for treatment of TNF-mediated diseases
     Miller, Karen; Diu-Hercend, Anita; Hercend, Thierry; Lang, Paul; Weber,
IN
     Peter; Golec, Julian; Mortimore, Michael
     Vertex Pharmaceuticals Incorporated, USA
PA
      PCT Int. Appl., 268 pp.
SO
      CODEN: PIXXD2
DT
      Patent
      English
LА
FAN.CNT 1
                                                                              DATE
                                     DATE
                                                   APPLICATION NO.
                             KIND
      PATENT NO.
                             _ _ _
                                                   WO 2003-US12262
                                                                              20030417
     WO 2003088917
                              A2
                                     20031030
PΙ
                                     20040304
                             A3
     WO 2003088917
              AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
               CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
               GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
               LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM,
               PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT,
          PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
                                                                              20030417
      US 2004048797
                                     20040311
                                                   US 2003-419327
                              A1
                                     20050126
                                                   EP 2003-721795
                                                                               20030417
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                              A2
               AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
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                              Ρ
                                     20020419
PRAI US 2002-374434P
                              W
                                     20030417
      WO 2003-US12262
      The invention discloses methods for identifying compds. useful for
AB
      regulating TNF-\alpha levels and/or activity. The invention also
      discloses methods for decreasing TNF-\alpha levels and/or activity.
      Compds. and compns. of the invention are useful for treating TNF-mediated
      diseases. The invention further discloses kits comprising the compds. and
      compns. herein and a tool for measuring TNF-\alpha activity and/or
      levels. Preparation of selected compds., e.g.
[3S/R, (2S)]-5-fluoro-4-oxo-3-[(1-
      (phenothiazine-10-carbonyl)piperidine-2-carbonyl)amino]pentanoic acid, is
      described.
      344461-03-6 344461-10-5 618459-84-0
ΙT
      618459-95-3 618460-05-2 618460-08-5
      618460-10-9 618460-11-0 618460-12-1
      RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
      (Biological study); USES (Uses)
          (TNF-\alpha modulator compound identification methods, and use for
         treatment of TNF-mediated diseases)
RN
      344461-03-6 CAPLUS
      Pentanoic acid, 5-fluoro-4-oxo-3-[[(2S)-1-oxo-2-(1-oxo-2(1H)-
CN
      isoquinolinyl)propyl]amino]- (9CI) (CA INDEX NAME)
```

RN 344461-10-5 CAPLUS

CN Benzoic acid, 2,6-dichloro-, (3S)-4-carboxy-2-oxo-3-[[1-oxo-2-(1-oxo-2(1H)-isoquinolinyl)propyl]amino]butyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 618459-84-0 CAPLUS

CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-5-fluoro-4-oxo-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 618459-95-3 CAPLUS

CN Pentanoic acid, 5-fluoro-4-oxo-3-[[(2S)-1-oxo-2-(1-oxo-2(1H)-isoquinolinyl)pentyl]amino]- (9CI) (CA INDEX NAME)

RN 618460-05-2 CAPLUS

CN Pentanoic acid, 5-fluoro-4-oxo-3-[[(2S)-1-oxo-2-[1-oxo-7-(trifluoromethyl)-2(1H)-isoquinolinyl]butyl]amino]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 618460-08-5 CAPLUS

CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-4-oxo-5-(2,3,5,6-tetrafluorophenoxy)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 618460-10-9 CAPLUS

CN Pentanoic acid, 5-fluoro-4-oxo-3-[[(2S)-1-oxo-2-[1-oxo-7-(propylthio)-2(1H)-isoquinolinyl]butyl]amino]-, mono(trifluoroacetate) (9CI) (CA INDEX NAME)

CM 1

CRN 618460-09-6 CMF C21 H25 F N2 O5 S Absolute stereochemistry.

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 618460-11-0 CAPLUS

CN Pentanoic acid, 5-fluoro-4-oxo-3-[[(2S)-1-oxo-2-(1-oxo-7-phenyl-2(1H)-isoquinolinyl)butyl]amino]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 618460-12-1 CAPLUS

CN Pentanoic acid, 4-oxo-3-[[(2S)-1-oxo-2-(1-oxo-2(1H)-isoquinolinyl)butyl]amino]-5-(2,3,5,6-tetrafluorophenoxy)-, (3S)- (9CI) (CA INDEX NAME)

```
ANSWER 5 OF 5 CAPLUS COPYRIGHT 2005 ACS on STN
L6
                 CAPLUS
AN
     2003:656594
     139:191460
DN
ΤI
     Phospholipids as caspase inhibitor prodrugs
·IN
     Mortimore, Michael; Golec, Julian M. C.
     Vertex Pharmaceuticals Incorporated, USA
PA.
SO
     PCT Int. Appl., 256 pp.
     CODEN: PIXXD2
DT
     Patent
LΑ
     English
FAN.CNT 1
     PATENT NO.
                         KIND
                                DATE
                                            APPLICATION NO.
                                                                    DATE
                                20030821
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             PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ,
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     US 2004019017
                          A1
                                20040129
                                            US 2003-366192
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     EP 1485107
                          Α1
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                                            EP 2003-739810
                                                                    20030211
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PRAI US 2002-355889P
                          Ρ
                                20020211
     WO 2003-US4457
                          W
                                20030211
     MARPAT 139:191460
OS
     The invention relates to compds. which are prodrugs of caspase inhibitors
AB
     and pharmaceutically acceptable salts thereof. The invention further
     relates to the release of caspase inhibitors from these compds. through
     selective bond cleavage. The invention further relates to pharmaceutical
     compns. comprising these compds., which are particularly well-suited for
     treatment of caspase-mediated diseases, including inflammatory and
     degenerative diseases. The invention further relates to methods for
     preparing compds. of this invention.
IT
     582317-55-3
     RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
     (Biological study); USES (Uses)
        (phospholipids as caspase inhibitor prodrugs)
RN
     582317-55-3 CAPLUS
     Pentanoic acid, 5-fluoro-4-oxo-3-[[1-oxo-2-(1-oxo-2(1H)-
CN
```

isoquinolinyl)propyl]amino]-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD RE.CNT 3 ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> dis 15 bib abs

- ANSWER 1 OF 1 CAPLUS COPYRIGHT 2005 ACS on STN
- 2001:435047 CAPLUS AN
- DN 135:46192
- Synthesis and use of heterocyclic substituted-amido halopentanoate ΤI derivatives as caspase inhibitors
- Golec, Julian; Charifson, Paul; Charrier, Jean-Damien; Binch, Hayley IN
- PΑ Vertex Pharmaceuticals Incorporated, USA
- PCT Int. Appl., 88 pp. SO CODEN: PIXXD2
- Patent DT

GI

	English CNT 1						
rAM.	PATENT NO.	KIND DA	ATE A	PPLICATION NO.	DATE		
ΡI	WO 2001042216			O 2000-US33260	20001208 <		
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				MD, RU, TJ, TM	•		
				SZ, TZ, UG, ZW,			
	DE, DK,	ES, FI, FR, C	GB, GR, IE,	IT, LU, MC, NL,	PT, SE, TR, BF,		
	BJ, CF,			ML, MR, NE, SN,			
	CA 2393710				20001208 <		
	BR 2000016282	A 20	0020827 B	R 2000-16282	20001208 <		
	EP 1244626	A2 20	0021002 E	P 2000-988026	20001208 <		
	R: AT, BE,	CH, DE, DK, B	ES, FR, GB,	GR, IT, LI, LU,	NL, SE, MC, PT,		
	IE, SI,	LT, LV, FI, I	RO, MK, CY,	AL, TR			
	JP 2003516393	T2 20	0030513 J	P 2001-543517	20001208		
	NZ 519424	A 20	0040326 N	Z 2000-519424	20001208		
	ZA 2002004390	A 20	0030602 Z	A 2002-4390	20020531		
	NO 2002002656	A 20	0020806 N	0 2002-2656	20020605 <		
PRAI	US 1999-169812P	P 19	9991208				
	WO 2000-US33260	W 20	0001208				
os	MARPAT 135:46192	2					

$$\bigcap_{N} \bigcap_{H} \bigcap_{O} F$$

Compds. I and their synthesis are claimed [wherein; R1 = H, CN, CHN2, AB (substituted)alkyl, aryl, non-aromatic heterocycle, etc.; R2 = CH2COOH, COOH (or ester/amide/isosteres of); R3 = H or alkyl; X1, X3 = N or C; X2 = bond, O, S, N or C wherein any X with suitable valence may bear a substituent; each C in ring A may also be substituted; ring A substituents = H, halo, alkyl, aryl, OH, CN, etc.; A may also bear a fused ring]. Over 20 synthetic examples are given. For instance; substitution of bromoacetic acid Et ester with the corresponding isoquinolone followed by saponification and coupling to 3-amino-5-fluoro-4-hydroxypentanoic acid tert-Bu ester provided the hydroxy ester intermediate. Oxidation of the hydroxy ester followed by treatment with TFA yielded II as a white powder. Compds. of the invention are caspase inhibitors; data is provided for caspase-1,-3,-7 and caspase-8 inhibition (Ki). Also determined was inhibition of IL-1 β secretion from peripheral blood mononuclear cells and activity in a Fas ligand induced apoptosis assay. Compound II had Ki (M-1 s-1) of 248,000 for caspase-1, 130,000 for caspase-3 and an IC50 of 2.9 μM for IL-1 β secretion. Compds. I may be used as a component of immunotherapy for the treatment of cancer.

=> log y COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	30.14	191.68
DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-4.38	-4.38

STN INTERNATIONAL LOGOFF AT 12:51:54 ON 08 JUL 2005

=> dis 15 bib abs hitstr

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L5
     ANSWER 1 OF 1 CAPLUS COPYRIGHT 2005 ACS on STN
AN
     2001:435047 CAPLUS
DN
     135:46192
     Synthesis and use of heterocyclic substituted-amido halopentanoate
ΤI
     derivatives as caspase inhibitors
     Golec, Julian; Charifson, Paul; Charrier, Jean-Damien; Binch, Hayley
IN
     Vertex Pharmaceuticals Incorporated, USA
PA
     PCT Int. Appl., 88 pp.
SO
     CODEN: PIXXD2
DΤ
     Patent
LΑ
     English
FAN.CNT 1
                                            APPLICATION NO.
                                                                    DATE
     PATENT NO.
                         KIND
                                DATE
                         ____
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A2 WO 2000-US33260 20001208 <--PΙ WO 2001042216 20010614 WO 2001042216 A3 20020228 AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG 20001208 <--CA 2000-2393710 CA 2393710 AA 20010614 20001208 <--20020827 BR 2000-16282 BR 2000016282 Α 20001208 <--EP 2000-988026 EP 1244626 A2 20021002 AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR JP 2003516393 T2 20030513 JP 2001-543517 20001208 NZ 519424 Α 20040326 NZ 2000-519424 20001208 20030602 ZA 2002-4390 20020531 ZA 2002004390 Α NO 2002-2656 20020605 <---NO 2002002656 20020806 Α Ρ 19991208 PRAI US 1999-169812P W 20001208 WO 2000-US33260 MARPAT 135:46192 os GI

$$\begin{array}{c|c}
 & \circ & \circ \\
 & & \downarrow \\
 & \downarrow$$

Compds. I and their synthesis are claimed [wherein; R1 = H, CN, CHN2, AB (substituted)alkyl, aryl, non-aromatic heterocycle, etc.; R2 = CH2COOH, COOH (or ester/amide/isosteres of); R3 = H or alkyl; X1, X3 = N or C; X2 = bond, O, S, N or C wherein any X with suitable valence may bear a substituent; each C in ring A may also be substituted; ring A substituents = H, halo, alkyl, aryl, OH, CN, etc.; A may also bear a fused ring]. Over 20 synthetic examples are given. For instance; substitution of bromoacetic acid Et ester with the corresponding isoquinolone followed by saponification and coupling to 3-amino-5-fluoro-4-hydroxypentanoic acid tert-Bu ester provided the hydroxy ester intermediate. Oxidation of the hydroxy ester followed by treatment with TFA yielded II as a white powder. Compds. of the invention are caspase inhibitors; data is provided for caspase-1,-3,-7 and caspase-8 inhibition (Ki). Also determined was inhibition of IL-1 β secretion from peripheral blood mononuclear cells and activity in a Fas ligand induced apoptosis assay. Compound II had Ki (M-1 s-1) of 248,000 for caspase-1, 130,000 for caspase-3 and an IC50 of 2.9 μM for IL-1 β secretion. Compds. I may be used as a component of immunotherapy for the treatment of cancer.

IT 344461-03-6P 344461-10-5P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(synthesis and use of heterocyclic substituted-amido halopentanoate derivs. as caspase inhibitors)

RN 344461-03-6 CAPLUS

CN Pentanoic acid, 5-fluoro-4-oxo-3-[[(2S)-1-oxo-2-(1-oxo-2(1H)-isoquinolinyl)propyl]amino]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 344461-10-5 CAPLUS

CN Benzoic acid, 2,6-dichloro-, (3S)-4-carboxy-2-oxo-3-[[1-oxo-2-(1-oxo-2(1H)-isoquinolinyl)propyl]amino]butyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

IT 344461-30-9P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(synthesis and use of heterocyclic substituted-amido halopentanoate derivs. as caspase inhibitors)

RN 344461-30-9 CAPLUS

CN Benzoic acid, 2,6-dichloro-, (3S)-5-(1,1-dimethylethoxy)-2,5-dioxo-3-[[1-oxo-2-(1-oxo-2(1H)-isoquinolinyl)propyl]amino]pentyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

=> log y COST IN U.S. DOLLARS	SINCE FILE	TOTAL
	ENTRY	SESSION
FULL ESTIMATED COST	7.28	168.82
DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-0.73	-0.73

STN INTERNATIONAL LOGOFF AT 12:57:55 ON 08 JUL 2005